Cognitive Neurorehabilitation

Edited by

Donald T. Stuss

Rotman Research Institute,
Baycrest Centre for Geriatric Care, Toronto, Canada
University of Toronto

Gordon Winocur

Rotman Research Institute,
Baycrest Centre for Geriatric Care, Toronto, Canada
Trent University and University of Toronto

and

Ian H. Robertson

Department of Psychology, Trinity College,
Dublin, Ireland

CAMBRIDGE
UNIVERSITY PRESS

PUBLISHED BY THE PRESS SYNDICATE OF THE UNIVERSITY OF CAMBRIDGE
The Pitt Building, Trumpington Street, Cambridge, United Kingdom

CAMBRIDGE UNIVERSITY PRESS
The Edinburgh Building, Cambridge CB2 2RU, UK www.cup.cam.ac.uk
40 West 20th Street, New York, NY 10011–4211, USA www.cup.org
10 Stamford Road, Oakleigh, Melbourne 3166, Australia
Ruiz de Alarcón 13, 28014 Madrid, Spain

First published 1999

Printed in the United Kingdom at the University Press, Cambridge

Typeset in Utopia 8/12pt in QuarkXPress™ [SE]

A catalogue record for this book is available from the British Library

Library of Congress Cataloguing in Publication data

Cognitive neurohabilitation / edited by Donald T. Stuss, Gordon
Winocur, and Ian H. Robertson.
p. cm.
Includes index.
ISBN 0 521 58102 8 hb
1. Cognition disorders–Patients–Rehabilitation. 2. Brain
damage–Patients–Rehabilitation. I. Stuss, Donald T.
II. Winocus, Gordon. III. Robertson, Ian. 1951– .
RC553.C64C654 1999
617.4′810443–dc21 98–43624 CIP

ISBN 0 521 58102 8 hardback

Contents

Part II Pharmacological approaches

Part III Clinical and management issues

Part IV Neurorehabilitation techniques

1

Neuroplasticity and recovery of function after brain injury

Bryan Kolb and Robbin Gibb

Introduction

Perhaps the most significant and perplexing question concerning the clinical neuropsychological investigation of the patient with brain injury relates to the issue of how to repair the injured nervous system in order to restore lost functions. It has long been known that damage to specific regions of cerebral cortex causes a change both in the remaining brain and in behaviour (for a review, see Kolb and Whishaw, 1996). Until recently, it was commonly believed that the adult mammalian cortex was structurally static, providing little opportunity for behavioural recovery following cortical injury. Evidence has begun to accumulate, however, suggesting that at least some cortical circuits might be modifiable following cortical injury. (This property of modifiability of neurons is often referred to as neuroplasticity, or plasticity.) It follows that if neural circuits can be modified after injury, then one might anticipate some type of functional change as well. In principle, there are three ways that the brain could show plastic changes that might support recovery.

Recovery could result from the reorganization of remaining circuits

The general idea is that the nervous system could reorganize in some way to do 'more with less'. It seems unlikely, however, that a complexly integrated structure like the cerebral cortex could undergo a wholesale reorganization of cortical connectivity, at least in the adult. Rather, recovery from cortical injury would be most likely to result from a change in the intrinsic organization of local cortical circuits in regions directly or indirectly disrupted by the injury. It should be noted, however, that it might be possible to produce significant reorganization of cortical connectivity in the young brain, especially if cortical development were incomplete, and for this potentiated alteration of connectivity to support more recovery than is seen in adults. For example, as the brain of the infant animal develops, it must produce millions of interconnections between brain cells. If the brain is injured during this period of connective growth, it should be possible to reorganize or replace many of the lost connections. A simple analogy might be that if the main trunk of a tree is damaged early in life, the tree can adapt by growing a new trunk. Similar injury in a mature tree will not be as easily repaired.

Cerebral reorganization could be stimulated by the exogenous application of different treatments

This could take the form of some sort of behavioural therapy or it might involve the application of some sort of pharmacological treatment that would influence reparative processes in the remaining brain. Once again, it would seem most likely that the induced neuronal changes would be in the intrinsic organization of the cortex. One might predict that the changes are likely to be more extensive than in the case of endogenous change, in part because the treatment could act upon the whole brain. To pursue the injured-tree metaphor, if the tree were given fertilizer and extra water, the effect of this therapy would be observed over the entire tree.

It should be possible, at least in principle, to replace lost neurons and at least some functions

This logic has led to considerable work on neural transplantation (e.g. Dunnett and Bjorkland, 1994), although the utility of this approach is far from proven. There is, in addition, another and even less developed possibility: it may be possible to stimulate the injured brain to replace its own neurons. This route is far more speculative but recent findings are encouraging. (This topic is also dealt with in some detail in Chapter 2).

The remainder of this chapter summarizes findings from studies that provide evidence that morphological changes in the brain are correlated with behavioural restitution. It begins with consideration of the assumptions that underlie such an approach. Because we presume that mechanisms underlying reparative changes in the injured brain are likely to be observed in response to experience in the normal brain, consideration is then given to the nature of structural changes in the normal brain and their relation to behaviour. This is followed by a summary of endogenous changes in the injured brain, manipulation of these endogenous changes, and, finally, the role of neurotrophins in stimulating regeneration of injured or lost brain circuits. Throughout the chapter, the focus is on studies that have correlated changes in brain and behaviour in the same subjects, usually laboratory rats.

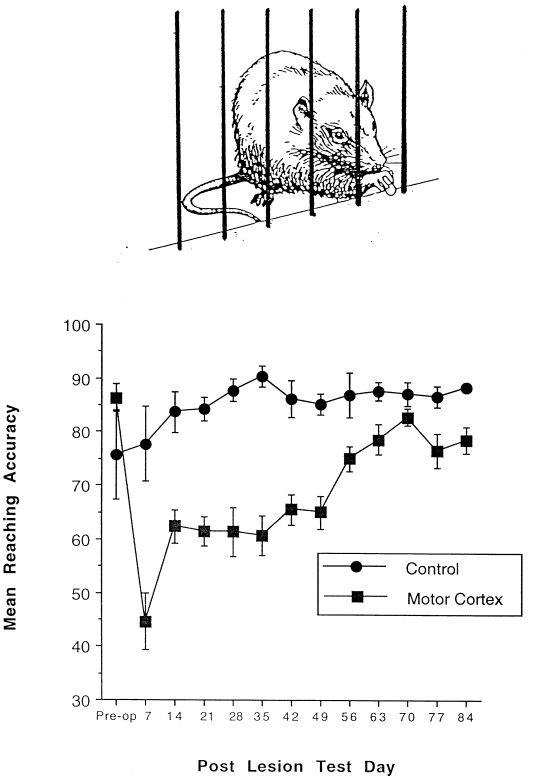

Fig. 1.1 *Top.* Illustration of the Whishaw reaching task. *Bottom.* Example of recovery of forelimb reaching accuracy after small motor cortex lesions.

Assumptions

- Restoration of function is possible after brain injury.
- Structural changes in the brain underlie behavioural change.

The authors must admit to three assumptions that strongly influence both their research and their interpretation of the research of others.

At least partial restoration of function can occur naturally after cerebral injury

Note that the assumption is not that there is a return of the original lost behaviour but rather that there is simply some form of restitution of lost function. This distinction is important because there is considerable debate over what constitutes recovery (e.g. Kolb, 1995). For the current purposes, recovery is defined as an improvement in function over time. Consider the following two examples.

Figure 1.1 illustrates the Whishaw reaching task in which rats are trained to reach through bars to obtain small pieces of food. Like people, rats excel in the use of their forelimbs and forepaws to retrieve quite small objects. The Whishaw task therefore allows us to study recovery of a behaviour that is commonly disrupted after cerebral injury in humans. In a typical study, rats were given small motor cortex lesions after training on the Whishaw task and were then retested at different intervals over the following weeks. Typically, such animals showed a slow improvement in their success at retrieving food by reaching with the affected limb. The

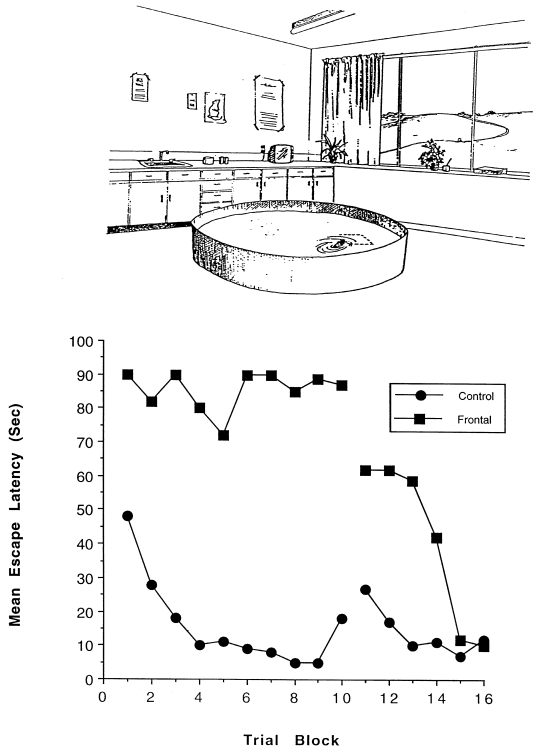

Fig. 1.2 *Top*. Illustration of the Morris water task. *Bottom*. Example of recovery of spatial navigation performance after medial frontal cortex lesions. Animals were first tested two weeks after surgery, given six months' recovery time, then retested. There is a dramatic improvement after six months' recovery.

performance of the animals never returned to normal levels, however, and, perhaps more importantly, when similar animals have been examined in other experiments by Whishaw and his colleagues, it has been shown clearly that the animals make markedly different movements (Whishaw et al., 1991). Thus, the apparent recovery in the reaching accuracy reflects not only some functional recovery but also behavioural compensation. Nonetheless, there is a behavioural change over time and this change is presumably associated with some form of neural modification.

Parallel results have been found in the Morris water task performance of rats with frontal cortex removals in adulthood (Fig. 1.2). In the Morris task, rats are placed in a large tank of murky water in which there is a small platform hidden just below the water surface. The rats' task is to learn to locate the hidden platform in order to escape from the water. Rats are aquatic animals and learn this task with ease. In contrast, rats with large bilateral frontal lesions are very poor at this task, in large part because their initial strategy of swimming around the perimeter of the pool is completely ineffective in finding the platform, which is located well away from the pool wall. Thus, when rats are trained two weeks after cortical injury they often fail to find the platform and swim around and around the pool until rescued. Even when the animals do locate the platform they appear to learn little about its location in the tank. In contrast, however, when the same animals are retrained six months later they are able to learn the task and can eventually perform surprisingly efficiently, although their navigation is never as accurate as that of control rats. Normal rats learn to swim directly to the platform, whereas rats with large frontal lesions learn a strategy to find the platform by swimming a fixed distance from the wall. With extended training, however, the rats with frontal lesions can learn the platform location. Thus, there is evidence of behavioural improvement in a 'motor task' such as forepaw reaching as well as in a 'cognitive task' such as the performance of a spatial navigation task. In neither case are the animals as proficient as intact control animals, but there is a clear improvement over time. One explanation for the behavioural improvement is that the animals have adapted to the cortical injury by using other, remaining cortical circuitry. The question is whether this circuitry has been modified in order to facilitate this behavioural improvement.

An understanding of the structural changes in the brain after injury is important for understanding how to stimulate functional recovery

Although this assumption is self-evident to most behavioural neuroscientists, it may not be as obvious to those who are preoccupied with the very real practical problems of helping brain-injured patients. Nonetheless, the key point here is that if we can understand which morphological changes are associated with functional recovery, then we can direct our attention to designing

treatments that will stimulate such plastic changes. An important corollary of this assumption is that if such plastic changes do not occur after an injury, then there will be an absence of functional recovery.

The mechanisms of cortical plasticity are most likely to be found at the synapse

Synaptic changes can be measured by analysis of either presynaptic or postsynaptic structure but it is the authors' view that the simplest way to correlate synaptic change and behaviour is to focus on the postsynaptic, or dendritic, side. This requires that the complete cell body and dendritic tree be stained, such as in a Golgi-type stain. Because the dendritic surface receives more than 95 per cent of the synapses on a neuron, it is therefore possible to infer changes in synapse number from measurements of dendritic extent and spine density (Fig. 1.3). One clear advantage of this measure is that one need not know a priori where to look because it is possible to stain, and to examine, the structure of cells throughout the entire brain. In addition, analysis requires only a light microscope (and a lot of time!). A strong bias of this review, therefore, will be towards studies that have utilized Golgi-type analyses of postsynaptic structure.

Finally, although the emphasis in most studies of structure–function relationships falls upon the analysis of neurons, there are solid grounds for looking at changes in the structure and number of glial cells. Glial cells play an important role in synaptic modification and thus can be a clue to the location and nature of experience-dependent changes in neurons and their synapses. The plasticity of glia can be analysed by estimating the number and types of glia as well as by measuring morphological characteristics such as soma size and the extent of arm-like protuberances. For example, when laboratory animals such as rats are placed in complex environments filled with novel 'toys' that they have an opportunity to interact with (so-called 'enriched environments'), there is a marked increase in the number and size of glial cells (e.g. Sirevaag and Greenough, 1991; Hawrylak and Greenough, 1995). This change in the glial cells is correlated with the changes in neuronal morphology and it is thought that the glial cells may play an important role in stimulating the neuronal changes.

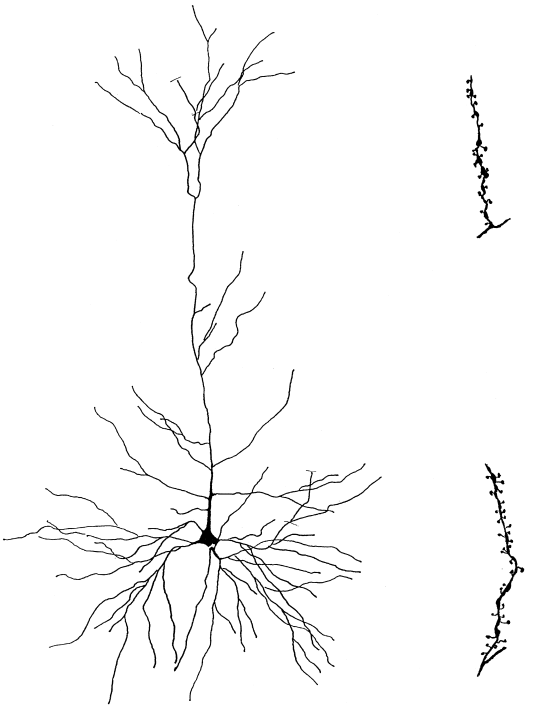

Fig. 1.3 Illustration of a typical pyramidal neuron and enlarged illustrations of spines on dendritic branches selected from different regions of the neuron.

Changes in the normal brain

- Neurons in the normal brain change their morphology during development and ageing.
- Neurons in the normal brain show specific changes in response to specific environmental experiences.

In order to understand the ways in which the injured brain changes, we must first consider the manner in which the uninjured brain changes. The logic here is that the nervous system is conservative, and plastic changes that occur in response to experience in the normal brain are likely to be recruited in the attempt to repair the abnormal brain. There are two principal types of changes in the normal brain (1) changes during brain development; and, (2) experience-dependent changes.

Neuronal changes during development

The mammalian brain follows a general pattern of development, beginning as a hollow tube in which a thin layer of presumptive neural cells surrounds a single ventricle. The development of the brain from the neural tube involves several stages, including: cell birth (mitosis), cell migration, cell differentiation, dendritic and axonal growth, synaptogenesis, and cell and synaptic death. The order of these events is similar across species, but because the gestation time varies dramatically across different mammalian species, the timing of the events relative to birth varies considerably. This can be seen in the common observation that, whereas kittens and puppies are born helpless and blind (their eyes do not open for about two weeks), human babies are born somewhat more mobile and with open eyes, whereas calves at birth are able to stand and walk about and, of course, have their eyes open. It is worth noting that rats, which are the subject of choice in most plasticity and recovery studies, are born even less mature than kittens and their eyes do not open until about postnatal day 15. They are weaned at around 21 days of age, reach adolescence at about 60 days, and can be considered adults by about 90 days. Thus, as we compare the effects of brain injury in infant laboratory rats and human infants, we need to consider the precise nature of the developmental events underway at the time of injury. Figure 1.4 summarizes a tentative timetable for comparing rats and people.

There are two aspects of neural development that are especially important in the current context. First, the cells from which the nervous system is derived are referred to as stem cells. Stem cells give rise to the cells that subsequently form particular body structures. For example, there are stem cells for blood, stem cells for the liver, and stem cells for the nervous system. If we fall and scrape our skin, we generate new cells by a process in which the skin stem cells generate new skin cells. Neural stem cells remain in the adult mammalian brain and thus provide the potential source of new cells to replace those lost to injury or diseases (for a review of the evidence for neural stem cells in adults, see Weiss et al., 1996). The challenge is to find the switch to turn on controlled cell production when it is needed. The second important aspect of neural development is the development of synapses. As neurons reach their final destination, they begin to develop axons and dendrites that will form synapses. Axons must not only grow but their growth must be directed towards appropriate targets. Dendrites do not have the same 'spatial navigation' problems of axons but they do form characteristic spatial patterns of branching. For instance, pyramidal cells, which are the primary output cells of the brain, have an easily recognizable pattern that is characterized by a vertical stalk (the apical stalk) with lateral branches that are reminiscent of branches off a tree trunk (see Fig. 1.3). In addition, there are basilar branches that grow laterally from the cell body and, like the apical stalk, they also have further branches (see Fig. 1.3). The apical and basilar fields are normally analysed separately because they typically have markedly different connections. Both the apical and basilar branches are covered with spines that form later. Both axons and dendrites grow rapidly during development and can also show remarkable plasticity in adulthood as dendrites can form spines and axons can form new axon terminations in hours and possibly even minutes. Note that the growth of new axonal arborizations does not represent the growth, de novo, of a long fibre from the cell body but is more likely to involve simply the growth of either

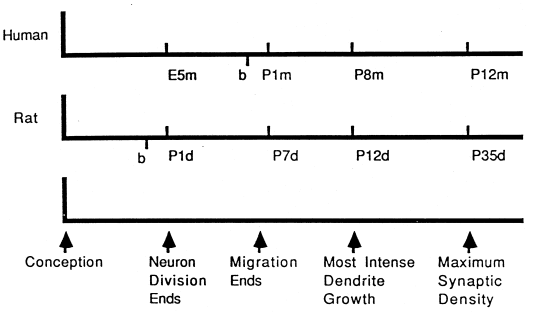

Fig. 1.4 Schematic illustration of the comparable developmental ages of the brain of the rat and human. E, embryonic day; P, postnatal day; b, day of birth. Note that the day of birth in the rat is much earlier in embryonic development than the day of birth in the human. Rhesus monkeys are born even more developed than humans.

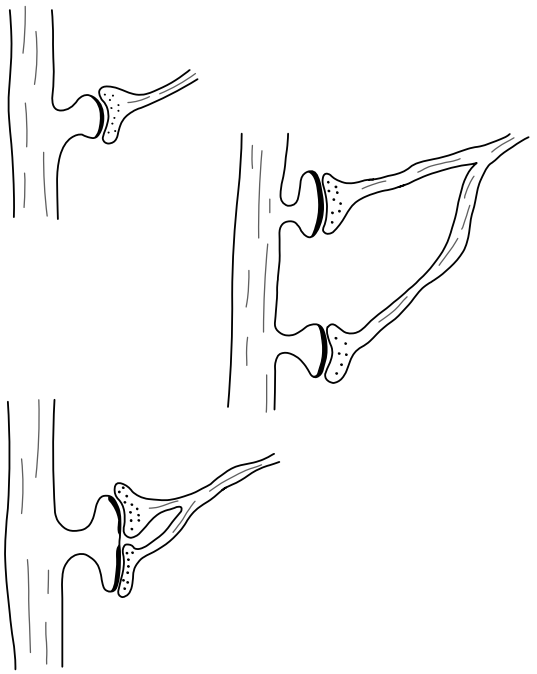

Fig. 1.5 Illustration of probable mechanisms of synapse formation. *Top*. A single synapse from an axon terminal. *Middle*. The axon terminal splits and forms two distinct synapses on two spatially separated spines. *Bottom*. The axon terminal splits and forms two synapses on the same spine.

additional end feet or connections en passant, as illustrated in Fig. 1.5.

Experience-dependent changes

It has long been assumed in the psychological literature that experiences in early childhood have greater effects upon later behaviour than do similar experiences in adulthood. The analysis of dendritic changes following exposure to enriched environments suggests that there is a structural basis to this differential effect of early experience on behaviour (e.g. Kolb et al., 1998). For example, the authors constructed 'rat condominiums', which are large enclosures ($1.2 \times 1.2 \times 2.5$ m high) with various runways, sticks, and miscellaneous toys, the latter being changed weekly. Rats were housed in same-sex groups of six for three months, beginning at weaning (21 days of age), at young adulthood (four months of age), or in senescence (two years or older). It was found that the age at which animals were placed in the enriched environments had qualitatively different effects upon dendritic structure. Rats placed into the complex environments versus standard laboratory housing in young adulthood showed effects similar to those reported by others: there was a large increase in dendritic length relative to cage-housed control rats. In addition, there was a small increase in spine density. Together, these dendritic changes would reflect a substantial increase in synapse number, a result that confirmed electron microscope studies by Greenough and his colleagues (e.g. Greenough and Chang, 1988). Parallel results were seen in senescent animals, as they showed significant increases in dendritic length and spine density relative to age-matched control rats. In contrast, when the changes in animals that were placed in the complex environments as juveniles were analysed, there was an increase in dendritic branching but a consistent decrease in spine density. That is, in comparison to older rats, the young rats showed a qualitatively different change in the distribution of synapses on pyramidal neurons. They had longer dendrites with spines placed further apart. Although the synapse number has not actually been counted, it seems likely that the young rats may actually have fewer synapses than the older ones. In contrast, however, these animals have the potential to add new spines quickly because there is space available. This capacity presumably reflects the increased potential for these animals to learn new information later.

The differential effect of enrichment in the young versus older rats led the authors to look at the effects of environmental manipulation even earlier in the rats' lives. It has been shown that tactile stimulation of premature human babies with a brush leads to faster growth and earlier hospital discharge (e.g. Solkoff and Matuszak, 1975; Field et al., 1986; Schanberg and Field, 1987). In addition, studies in infant rats have shown that similar treatment alters the structure of olfactory bulb neurons and has effects on later olfactory-guided behaviour (e.g. Coopersmith and Leon, 1984; Leon, 1992). Infant rats were therefore stroked with a camel-hair paintbrush three times daily from day 7 to day 21 of life.

Animals were subsequently raised in standard laboratory cages and were sacrificed in adulthood. Golgi analysis revealed that the early experience had no effect upon dendritic length in adulthood but there was a significant drop in spine density (Kolb et al., 1997b). Curiously, this anatomical change was correlated with significant improvement in the performance of animals in both the Whishaw reaching task and Morris water task. Thus, we see that experience can alter the brain's structure and function.

These results lead to several conclusions. First, 'enriched' experience can have very different effects upon the brain at different ages. Second, experience not only leads to 'more' but can also lead to 'less'. That is, although there is a temptation to presume that experiences lead to increased numbers of synapses and probably to increases in glia, it appears that there may be either increases or decreases, the details varying with age at experience. Third, changes in dendritic length and dendritic spine density are clearly dissociable. It is not immediately clear what the differences mean in terms of neuronal function but it is clear that experience can alter these two measures independently and in different ways at different ages. Finally, because the changes in neural structure that are associated with experience are correlated with more proficient production of a variety of behaviours, it is reasonable to expect that similar changes might be observed in animals with cerebral injuries. Note, however, that there is not a single change to look for in the injured brain but rather several different types of changes.

Evidence of morphological changes in the human brain

The idea that morphological change is associated with functional change is central to the thrust of this chapter. It is reasonable to ask in the context of the rehabilitation of humans, however, if there is any evidence for anatomical–functional correlations in humans. Such studies are difficult to carry out because they require the availability of postmortem tissue from people whose behaviour was characterized premorbidly. Recently, Scheibel and his colleagues have published a series of papers that are germaine to this question.

For example, Jacobs, Schall and Scheibel (1993) found a relationship between the extent of dendritic arborization in a cortical language area (Wernicke's area) and amount of education. Hence, the cortical neurons from the brains of deceased people with university education had more dendritic arbor than those from people with high school education who, in turn, had more dendritic material than those with less than high school education. Of course, it may have been that people with larger dendritic fields were more likely to go to university but that is not easy to test. In another study, Jacobs et al. (1993) took advantage of the now well-documented observation that females have verbal abilities that are superior to those of males (for a review, see Kolb and Whishaw, 1996). Their hypothesis was that this might be reflected in a sex difference in the structure of cortical neurons, and it was: females have more extensive dendritic arbors than males. Furthermore, this sex difference was present as early as age nine, suggesting that such sex differences emerge within the first decade.

Scheibel et al. (1990) approached the matter in a slightly different way. They began with two hypotheses. First, they suggested that there is a relationship between the complexity of dendritic arbor and the nature of the computational tasks performed by a brain area. To test this hypothesis they examined the dendritic structure of neurons in different cortical regions that they proposed to have functions that varied in computational complexity. For example, when they compared the structure of neurons corresponding to the somatosensory representation of the trunk versus the structure of those for the fingers, they found the latter to have more complex cells. They reasoned that the somesthetic inputs from receptive fields on the chest wall would constitute less of an integrative and interpretive challenge to cortical neurons than those from the fingers and thus the neurons representing the chest were less complex. Similarly, when they compared the cells in the finger area to those in the supramarginal gyrus, a region that is associated with higher cognitive processes, they found the supramarginal gyrus neurons to be more complex.

The second hypothesis was that dendritic trees in all regions are subject to experience-dependent change. As a result, Scheibel et al. hypothesized that predominant

life experiences (e.g. occupation) should be reflected in the structure of dendritic trees. Although they did not test this hypothesis directly, they did make an interesting observation. In their study comparing cells in the trunk area, the finger area, and the supramarginal gyrus, they found curious individual differences. For example, especially large differences in trunk and finger neurons were found in the brains of three people – a typist, a machine operator, and an appliance repairman. In each of these, a high level of finger dexterity maintained over long periods of time may be assumed. In contrast, one case with no trunk–finger difference was a salesman in whom one would not expect a good deal of specialized finger use. These results are suggestive, although we would agree with Scheibel et al.'s caution that 'a larger sample size and far more detailed life, occupation, leisure, and retirement histories are necessary' (p. 101). The preliminary findings in this study do suggest that such an investigation would be fruitful. Furthermore, taken together, the Scheibel studies suggest that, just as in laboratory animals, there are structural correlates of behavioural capacities in humans.

Endogenous change in the injured brain

- Cortical injury results in changes in dendritic fields of remaining neurons.
- Dendritic changes vary with age at injury.
- Dendritic changes are correlated with functional outcome.
- During development there are especially 'good' and 'bad' times for injury.

As a general rule of thumb, we can state that when neurons lose connections there is a retraction of dendritic processes and when neurons gain connections there is an extension of dendritic branches and/or an increase in spine density. Thus, when the brain is injured and neurons are lost there will be a decrease in connections for some neurons and, as the brain reorganizes, there will be a subsequent increase. For example, when frontal cortex was removed in adult rats, an initial drop in dendritic arborization in proximal cortical regions such as the parietal cortex was found. This atrophy slowly resolved and four months later there was a significant increase in dendritic morphology, which was correlated with the partial restitution of function on the Whishaw reaching task and Morris water task (e.g. Kolb, 1995). This type of compensatory change has been described after injury to both the neocortex and hippocampus (e.g. Steward, 1991; Kolb, 1995) and can probably occur after damage to subcortical regions as well.

Even more dramatic evidence of functional recovery correlated with dendritic growth can be seen in brains with injury during development. The first systematic studies showing better recovery from brain injury during infancy than in adulthood were done by Margaret Kennard, who studied the effects of motor cortex lesion in infant monkeys. Her seminal observation was that the animals with early lesions showed better recovery of motor functions than those with injuries in adulthood (e.g. Kennard, 1940). This observation was later termed the Kennard Principle by Teuber. Although Kennard did not study anatomical change, she predicted that there would be some sort of corresponding change in the remaining cortical cells, and the authors have shown this to be the case. Extensive frontal cortex lesions were made in infant rats at seven to ten days of age and it was shown that these animals had dramatic functional recovery in adulthood (e.g. Kolb and Whishaw, 1981), a phenomenon consistent with the Kennard Principle. It was then shown that this functional recovery, which was measured both on neuropsychological learning tasks as well as on motor behaviours, was correlated with a dramatic increase in dendritic length as well as an increase in dendritic spine density (for a review, see Kolb, 1995). Thus, as in adult rats, functional recovery was correlated with dendritic growth. However, in contrast to the effects of injury in adult animals, the changes in the young animals were far more widespread and could be found throughout the neocortex (e.g. Kolb, Gibb and van der Kooy, 1994). For example, anomalous connections were found from the prefrontal and motor regions to the striatum. Similarly, there were abnormal projections from the mesencephalic dopaminergic zones to the parietal cortex. In other words, functional recovery after early brain damage is correlated with more widespread changes in cortical connectivity than after similar injury in adulthood. This young versus old difference in plasticity

probably accounts for the Kennard effect. Enhanced dendritic changes are not unique to animals with frontal lesions as similar results have been found in animals with occipital lesions, temporal lesions, motor lesions, and hemidecortications (for a review, see Kolb, 1995).

It was noted earlier that if dendritic growth plays a role in recovery of function, then in the absence of dendritic growth we should not see recovery. Indeed, this is the case. Hebb (1949) postulated that brain injury early in life will, under some circumstances, result in more severe behavioural disruption than similar damage later in life. In other words, Hebb proposed what is essentially the opposite of the Kennard Principle. He based his hypothesis on his observation that children with perinatal injuries to the frontal lobe appeared to fare worse in adulthood than children with injuries later in life or in adulthood. As the authors manipulated the age of their animals with frontal removals in infancy, it was found that when removals were made earlier than seven days, and especially in the first four days of life, animals were produced whose behavioural outcome was dismal relative to that of animals with similar lesions in adulthood and, of course, relative to those with similar injuries just a few days later. Such animals were not capable of learning the Morris task, even with extensive training, and they could not reach for food in the Whishaw reaching task. Dendritic analysis revealed that, in contrast to the increased dendritic growth in the rats with removals on days seven to ten, these animals had a marked atrophy of dendritic arbor and a decrease in spine density (Fig. 1.6). Hence, whereas the animals with lesions around ten days of age had an increase in cortical synapses that was correlated with dramatic recovery, animals with lesions at one to four days of age had a decrease in cortical synapses that was correlated with an absence of recovery. Indeed, such animals performed more poorly on most of the behavioural tests than animals with similar injuries in adulthood. This is reminiscent of the retardation seen after injuries in the third trimester in humans. It is known that children with various forms of retardation show a decrease in the density of dendritic spines, which are the point of synapse of the majority of excitatory synapses on pyramidal neurons. When changes in spine density after the early lesions were analysed, it was found that spine density increased after day ten lesions and, like the retarded children, it decreased after day one lesions. Curiously, it was found that changes in spine density and dendritic growth could be dissociated: frontal lesions at seven days of age resulted in partial functional recovery (Whishaw reaching task and other motor tasks, Morris water task) that was correlated with increased spine density but not with dendritic growth (Kolb, Stewart and Sutherland, 1997c). This is reminiscent of the authors' observations in the normal brain that showed that similar experiences at different ages could alter spine density, dendritic growth, or both. Thus, it appears that the brain recruits mechanisms to sustain learning and memory similar to those recruited to support functional recovery.

An absence of significant functional recovery can also be seen in adult rats with large unilateral devascularizing lesions including portions of motor, parietal, and anterior visual cortex. These animals have a severe and chronic impairment in various motor and cognitive tasks that is correlated with a permanent atrophy of remaining cortical neurons (Kolb et al., 1997a). This result is interesting because the lesion mimics the effects of large middle cerebral artery strokes in humans. Thus, it may be that the reason for such dismal recovery in people with these strokes is that the rest of the hemisphere fails to compensate.

Manipulation of endogenous change

- Behavioural treatments stimulate dendritic growth and potentiate recovery.
- Behavioural treatments provide the greatest benefit for those with the least naturally occurring recovery.
- Pharmacological treatment with neurotrophins stimulates dendritic growth and functional growth.

It has been seen that if a cerebral injury is followed by an increase in dendritic space there is a good functional outcome, whereas if an injury leads to an atrophy of dendritic space there is a poor functional outcome. It follows that if we can potentiate dendritic growth in animals showing poor recovery of function, we should enhance functional recovery. The treatments for the potentiated growth range from behavioural therapy to the application of some sort of pharmacological

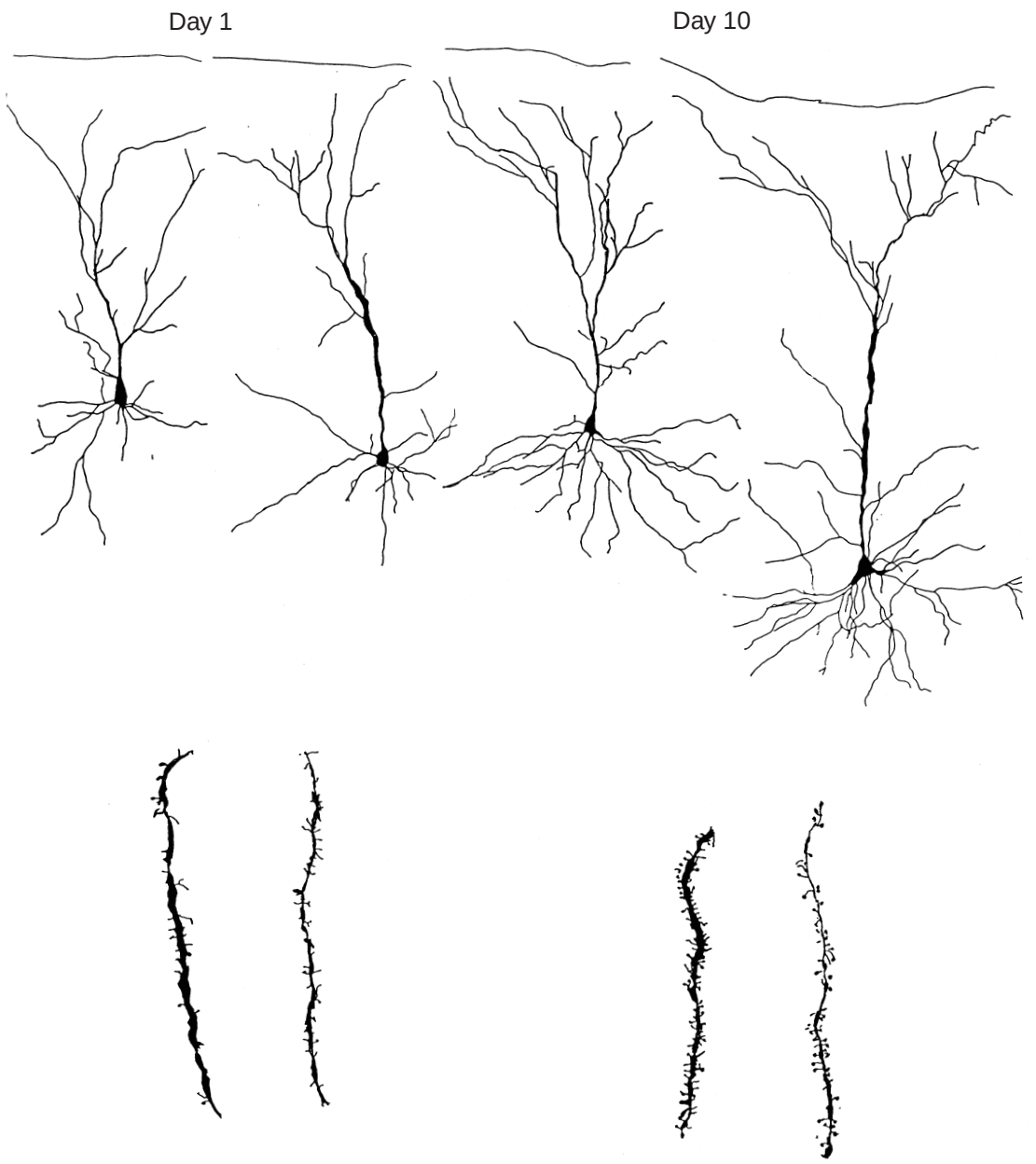

Fig. 1.6 *Top.* Camera lucida drawings of representative neurons from the parietal cortex of an adult rat with a medial frontal lesion on day one or day ten. The neurons from day ten brains have far more extensive dendritic arborization than neurons from day one brains. *Bottom.* Camera lucida drawings of segments of the terminal dendrites from cells from the same brains as illustrated in the top figure. There is a clear difference in the density of dendritic spines.

treatment. The pharmacological treatments could be of various forms, including growth factors (e.g. nerve growth factor, NGF), hormones (e.g. sex steroids), or chemicals that influence transmitters, especially the neuromodulators such as acetylcholine and noradrenaline. The focus here is on behavioural therapy and growth factors. (The role of sex hormones and neuromodulators is reviewed elsewhere: Kolb, 1995; Kolb et al., 1997a).

Behavioural therapy

Although it is generally assumed that behavioural therapies will improve recovery from cerebral injury in humans, there have been few direct studies of how this might work, when the optimal time for therapy might be, or even whether it actually is effective. Furthermore, as we try to develop animal models of cognitive or motor therapies, we are left with the problem of determining what an appropriate therapy might be. There have been many studies of the effects of various types of experience on functional outcome after cerebral injury in laboratory animals but the results have been inconsistent and generally disappointing (for reviews, see Schulkin, 1989; Will and Kelche, 1992). One difficulty with these studies is that few actually measured neuronal morphology; most focused primarily on functional outcome with different environmental manipulations. The authors' approach has been somewhat different. They have chosen behavioural manipulations that were known to be capable of changing the brain of intact animals and then exposed the brain-injured animals, especially those with poor functional outcomes, to the same experiences. The following illustration is from examples of the authors' work with rats with infant lesions. It was noted earlier that the developing brain is influenced by tactile stimulation during infancy and that the young animal is influenced by housing in enriched environments. Because the animal with a cortical lesion in the first days of life is functionally devastated in adulthood, and because it shows atrophy of cortical neurons, it was anticipated that such animals would benefit most from early experience.

In one series of studies, animals were given frontal or posterior parietal lesions at four days of age, followed by tactile stimulation (stroking) until weaning. The animals were group housed in laboratory cages and then tested on various tasks sensitive to frontal or parietal injury. For example, tests such as the Whishaw and Morris tasks were used to assess frontal injury and tests such as the landmark task (Kolb and Walkey, 1987) and tests of limb dexterity (Kolb and Whishaw, 1983) were used to assess parietal injury. The rats with tactile stimulation showed an unexpectedly large attenuation of the behavioural deficits of cerebral injury as a result of this rather brief 'therapy'. In fact, the rats with frontal lesions on day four showed a nearly complete recovery of performance in the Whishaw reaching task as they performed as well as control rats that had not been given the tactile experience. This was a stunning reversal of a devastating functional loss normally seen in animals with such injuries at this age. Analysis of the brains showed a reversal of the atrophy of the remaining cortical neurons normally associated with such early lesions and, more interestingly, a reversal of the decrease in spine density that is normally associated with the tactile stimulation. In other words, stroking leads to a decrease in spine density in normal animals but to an increase in spine density in the lesion animals. Thus, it is clear that not only can experience alter the brain, it can alter the normal and injured brain in different ways.

In another series of experiments, rats that had lesions on postnatal days one, five or seven were placed in enriched environments for three months, beginning at the time of weaning. It was anticipated that the animals with the earliest injuries would show the greatest functional benefit because the experience would reverse the neuronal atrophy. In contrast, it was expected that the animals with the best recovery would show the least benefit because their neurons had already grown after the injury. This was indeed the case. Rats with day one or day five lesions showed a dramatic reversal of functional impairments that was correlated with a reversal of dendritic atrophy (e.g. Kolb and Elliott, 1987). Animals with day seven lesions showed only a small enhancement of recovery and neural structure. The dramatic improvement in the animals with the earliest injuries carries an important message for it suggests that even the young animal with substantial neural

atrophy and behavioural dysfunction is capable of considerable neuroplasticity and functional recovery in response to behavioural therapy. The important remaining therapeutic questions relate to the nature of the most beneficial therapy and the optimal timing for initiating the therapy.

But what about the effects of therapeutic experience in adulthood? There is a considerable literature suggesting that specific training is generally not beneficial to laboratory animals with cerebral injuries, although there are exceptions (e.g. Will and Kelche, 1992). Few studies have actually looked at morphological and behavioural change, however. The authors would predict that behavioural therapies that changed the brain would enhance recovery whereas those treatments that did not change the brain would not influence recovery. They therefore made large frontal lesions in rats and then either placed them in the enriched environments or returned them to their standard laboratory cages (Kolb and Gibb, 1991). After two months of recovery and experience, the animals were tested on various behavioural tasks. The functional results were disappointing as only a limited benefit was found from the special housing in the brain-injured animals. This result made sense, however, when the neuronal morphology of the animals was analysed. Specifically, it was found that the enriched experience interacted with the lesion-induced changes in neuronal morphology. Thus, the frontal lesions stimulated an increase in dendritic arborization in parietal cortex but did not affect visual cortex. Enrichment had no additional effect on the parietal neurons but stimulated growth in the occipital neurons. It therefore appears that neuronal changes induced by the lesion may place limits upon the environment's capacity for further neuronal, and subsequently functional, change. Specifically, once having been altered in response to a frontal injury, adjacent parietal neurons may be unable to change further in response to experience.

Perhaps the best way to proceed at this time is to determine what types of behavioural treatment are most effective in changing the adult brain and then use such treatments to influence recovery. A series of studies by Black, Greenough and their colleagues (e.g. Black et al., 1987, 1990; Black, Polinsky and Greenough, 1989) is germaine. These authors trained animals to negotiate a complex obstacle course ('acrobat rats') or placed rats in running wheels where they obtained forced exercise. The animals in the wheels showed increased capillary formation in the cerebellum but no change in cerebellar Purkinje cell synapses, whereas the acrobat rats showed a 30 per cent increase in Purkinje synapses. Thus, merely increasing neuronal support does not change the neurons. The critical feature for neuronal change is presumably increased neuronal processing, which would be facilitated by a complementary increase in metabolic support. A critical experiment would be to train animals in running wheels, which would potentiate capillary growth in brain, and then to give the animals specific training. It could be predicted that animals with the metabolic support in place would show an enhanced benefit from the training and, more speculatively, animals with cerebral injuries would show even more benefit.

In sum, the effects of experience on the injured brain are complex and vary with precise age at injury as well as with the time of onset of experience. Nonetheless, the authors have shown that behavioural therapies do influence functional outcome from cortical injury and that this outcome is associated with changes in the morphology of cortical neurons. Perhaps the most important message is that the infant with the most miserable functional outcome is especially helped by behavioural therapy. This is an important lesson for the treatment of children with perinatal brain injuries.

Growth factors

Basic neurobiological research over the past decade has shown that there are several proteins that have the property of stimulating neuromitosis as well as synaptogenesis both during development and in adulthood. Two classes of such proteins have been identified (Table 1.1). These compounds have generated considerable interest because of their potential for the treatment of dementing diseases (e.g. Hefti et al., 1991) as well as for recovery from injuries (e.g. Hagg, Louis and Varon, 1993). One example of the effect of neurotrophic factors on recovery and dendritic growth is described.

It was mentioned earlier that rats given large

Table 1.1 Molecules exhibiting neurotrophic activities

Proteins initially characterized as neurotrophic factors
Nerve growth factor (NGF)
Brain-derived neurotrophic factor (BDNF)
Neurotrophin-3 (NT-3)
Ciliary neurotrophic factor (CNTF)
Growth factors with neurotrophic activity
Fibroblast growth factor, acidic (aFGF or FGF-1)
Fibroblast growth factor, basic (bFGF or FGF-2)
Epidermal growth factor (EGF)
Insulin-like growth factor (ILGF)
Transforming growth factor (TGF)
Lymphokines (interleukin 1, 3, 6 or IL-1, IL-3, IL-6)
Protease nexin I, II
Cholinergic neuronal differentiation factor

Notes:
For reviews see Hefti and Knusel (1991), and Hagg et al. (1993).

ischaemic lesions of the dorsolateral cortex have poor functional recovery and develop widespread atrophy of the dendritic fields of remaining cortical neurons. Nerve growth factor was administered to such animals via intraventricular cannulae (Kolb et al., 1997a). The major findings were that: (1) NGF stimulated dendritic growth and increased spine density in cortical pyramidal neurons in normal brains; (2) NGF stimulated partial functional recovery measured in the Whishaw reaching task; and, (3) this NGF-stimulated recovery was associated with increased dendritic growth and increased spine density (Fig. 1.7). The authors have now conducted parallel experiments with another neurotrophin, basic fibroblast growth factor (bFGF), which acts to increase the endogenous production of NGF, and have found analogous results (Rowntree and Kolb, 1997). These results are exciting because they imply that treatments with trophic factors can stimulate recovery from cortical injury and that this recovery is supported by morphological change in remaining cortical neurons (see also Chapter 2).

One of the difficulties in the use of trophic factors to treat brain-injured people is that they do not pass the blood–brain barrier easily. There is, therefore, considerable interest in developing compounds that might stimulate the brain to produce trophic factors. Recently, it has become evident that the production of trophic factors may be stimulated by experience. For example, it has been shown that animals placed in an enriched environment have increased bFGF activity if they subsequently have cortical injury (Kolb et al., 1997a). In other words, experience appears to stimulate the brain's endogenous bFGF reaction to an injury. This type of result provides a direct link between behavioural therapy, neuronal growth and trophic factors. Thus, it may be possible to enhance the effects of behavioural therapies by coadministration of trophic factors.

Stimulation of neural regeneration

- The infant rat brain is capable of spontaneous regeneration of lost neurons.
- Stimulation of the adult brain with neurotrophins may stimulate neurogenesis and functional recovery.

The demonstration that there are quiescent stem cells in the adult mammalian brain has important implications for the study of recovery of function (Weiss et al., 1996). Several studies have now shown that these cells can be removed from the adult human brain, placed in culture, and stimulated to divide and to produce both neurons and glia (Kirschenbaum et al., 1994). Furthermore, it now appears that at least two brain regions, the olfactory bulb and hippocampus, produce new neurons throughout the life of mammals, including primates (e.g. Altman and Bayer, 1993; Lois and Alvarez-Buylla, 1994). Thus, the mammalian brain not only has the potential to develop new neurons in adulthood but it actually does. In principle, it therefore should be possible to stimulate these cells to produce new neurons after an injury. There are, however, several practical problems for the nervous system. First, the neurons must get to the site of injury. Second, they must differentiate into the appropriate neuronal types. Third, they must develop the appropriate connections. In other words, the cells must replicate the normal sequence of brain development well after this development is complete. The question that arises is what is it that stimulates the brain to undergo this series of steps in the first place? One possibility is the presence of specific trophic factors. It follows that it might be possible to induce regrowth by

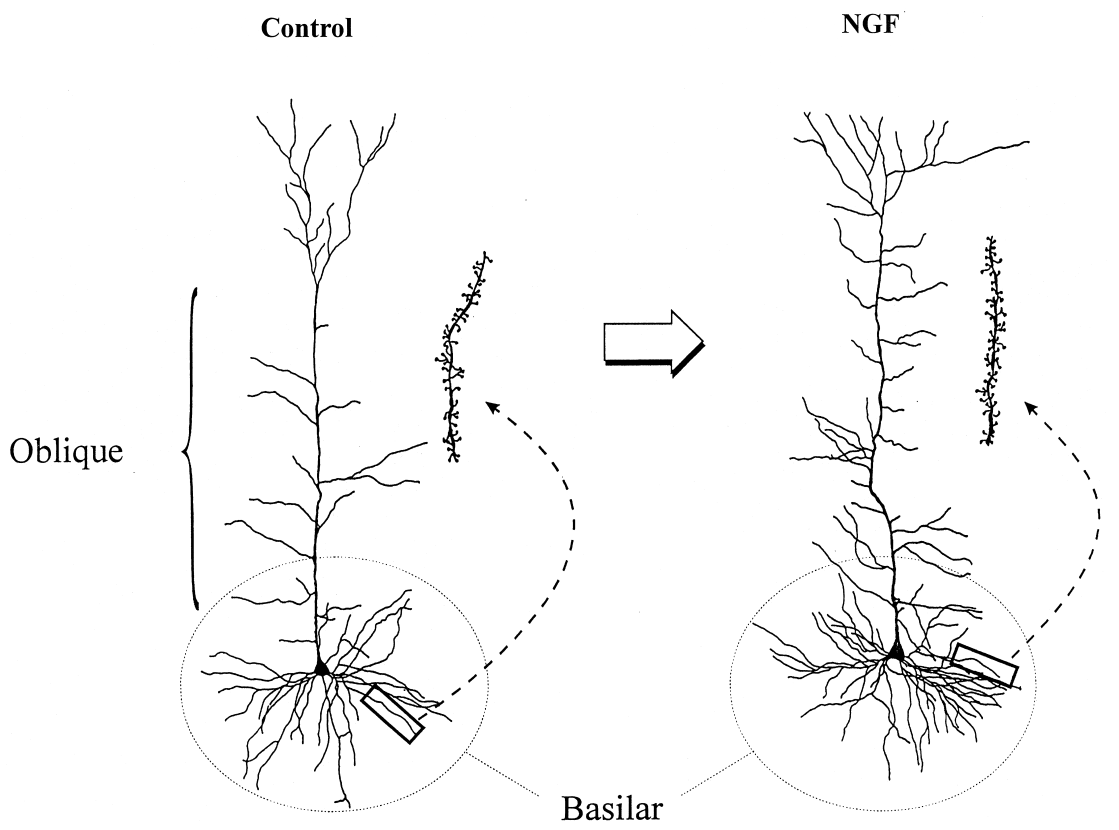

Fig. 1.7 Examples of layer V pyramidal cells taken from the cingulate cortex of a vehicle control rat (left) and an NGF-treated rat (right). The inset illustrates spine density in a typical terminal tuft from basilar fields. NGF treatment increased dendritic arborization and spine density in the terminal branches.

stimulating the brain with the appropriate growth factors. Of course, the brain is producing these during development so we might predict that the best time to stimulate the brain to regrow is when it is still growing. Recently, it has been demonstrated that this is the case (Kolb et al., 1997b).

In the course of studying rats with restricted lesions of midline frontal region in infancy, the authors noticed that there was no lesion cavity when the brains were examined in adulthood. Although this cavity loss might have been due to a mechanical shifting of the remaining neural tissue, the authors have now shown that the cavity fills with neurons that are born after the injury and that the new neurons develop appropriate connections with the rest of the brain. Furthermore, animals with this regrowth show virtually complete restitution of function and, if the regrowth process is blocked with a substance that interferes with stem cell activity, the recovery of function is blocked. This is an exciting discovery because it implies that not only is it possible to regrow lost neural regions, but also these neural regions are functional.

The demonstration of neuronal regeneration in the developing brain does not, however, prove that such a process is possible in the adult brain. Indeed, we know that even very small midline frontal lesions in adult brains do not lead to neurogenesis. It is hoped, however, that by providing the adult brain with appropriate

trophic factors that might mimic the signals present during development, it might be possible to stimulate cerebral regeneration in adults. The authors' preliminary studies show that by providing the brain with a mixture of trophic factors that might mimic the state during development, it is possible to stimulate the brain to produce new neurons and for these neurons to migrate to the lesion cavity. It has yet to be shown, however, that the newly generated neurons can support functional recovery.

Conclusions

1. At least partial restitution of function (i.e. recovery of function) is possible after cerebral injury. Functional restitution does not necessary imply the return of lost abilities but is more likely to reflect the development of compensatory strategies to cope with the lost neural circuits. The challenge for rehabilitation is to find ways to encourage the brain to develop these compensatory strategies.
2. Functional recovery after cerebral injury usually results from reorganization of remaining cortical circuits. This reorganization can be inferred from changes in the dendritic morphology of cortical neurons. Processes that serve to enhance advantageous morphological changes will lead to enhanced functional recovery, whereas processes that retard or prevent morphological change will interfere with functional recovery. It follows that the absence of recovery of function reflects an absence of sufficient reorganization of cerebral circuitry. Thus, one challenge for rehabilitation is to provide treatments that will stimulate the brain into making the necessary morphological adjustments.
3. The compensatory changes in neuronal morphology that underlie functional recovery are similar in nature to those that the brain uses normally during brain development and during the processes of learning and memory. Because the normal brain uses multiple experience-dependent changes to code experiences, we can expect multiple injury-dependent changes to underlie recovery of function. An understanding of the nature of normal experience-dependent changes is therefore critical to understanding the nature of processes underlying recovery of function.
4. Although the processes underlying experience-dependent change and injury-induced change may be similar, there is no guarantee that experience affects the uninjured brain in the same manner as the injured brain. Indeed, the fact that the brain is changing in response to injury means that the same experience may be acting on a fundamentally different neural substrate in the normal and injured brain.
5. The reorganization of remaining cortical circuits can be potentiated by the application of different treatments, including behavioural therapy, trophic factors, and other pharmacological agents. The enhanced reorganization of cortical circuits will lead to enhanced functional recovery. Different treatments may interact to enhance recovery. For example, behavioural therapies may act, in part, via their action in stimulating the endogenous production of trophic factors. Thus, combining behavioural therapies with the pharmacological administration of compounds to increase the availability of trophic factors may lead to enhanced functional outcome.
6. There are times during development when morphological changes, and subsequently functional recovery, are more likely to occur. For humans, the least favourable time is probably at the end of the gestational period and perhaps including the first month or so of life, whereas the most favourable time is likely to be at one to two years of age.
7. There is preliminary evidence to suggest that it may be possible to induce neural regeneration in the injured brain and that the regenerated brain functions to support functional recovery.

References

Altman, J. and Bayer, S. 1993. Are new neurons formed in the brains of adult mammals? A progress report, 1962–1992. In *Neuronal Cell Death and Repair*, ed. A.C. Cuello, pp. 203–25. New York: Elsevier.

Black, J.E., Greenough, W.T., Anderson, B.J. and Isaacs, K.R. 1987. Environment and the ageing brain. *Can J Psychol*, **41**, 111–30.

Black, J.E., Isaacs, K.R., Anderson, B.J., Alcantara, A.A. and Greenough, W.T. 1990. Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats. *Proc Natl Acad Sci USA* **87**, 5568–72.

Black, J.E., Polinsky, M. and Greenough, W.T. 1989. Progressive failure of cerebral angiogenesis supporting neural plasticity in ageing rats. *Neurobiol Aging* **10**, 353–8.

Coopersmith, R. and Leon, M. 1984. Enhanced neural response to familiar olfactory cues. *Science* **225**, 849–51.

Dunnett, S.B. and Bjorklund, A. (eds.) 1994. *Functional Neural Transplantation*. New York: Raven Press.

Field, T., Schanberg, S.M., Scafidi, F. et al. 1986. Tactile/kinesthetic stimulation effects on preterm neonates. *Pediatrics* **77**, 654–58.

Greenough, W.T. and Chang, F.F. 1988. Plasticity of synapse structure and pattern in the cerebral cortex. In *Cerebral Cortex*, Vol. 7, ed. A. Peters and E.G. Jones, pp. 391–440. New York: Plenum Press.

Hagg, T., Louis, J.-C. and Varon, S. 1993. Neurotrophic factors and CNS regeneration. In *Neuroregeneration*, ed. A. Gorio, pp. 265–88. New York: Raven Press.

Hawrylak, N. and Greenough, W.T. 1995. Monocular deprivation alters the morphology of glial fibrillary acidic protein-immunoreactive astrocytes in the rat visual cortex. *Brain Res* **683**, 187–99.

Hebb, D.O. 1949. *The Organization of Behaviour*, New York: Wiley.

Hefti, F., Brachet, P., Will, B. and Christen, Y. (eds.) 1991. *Growth Factors and Alzheimer's Disease*. Berlin: Springer-Verlag.

Hefti, F. and Knusel, B. 1991. Neurotrophic factors and neurodegenerative diseases. In *Growth Factors and Alzheimer's Disease*, ed. F. Hefti, P. Brachet, B. Will and Y. Christen, pp. 1–14. Berlin: Springer-Verlag.

Jacobs, B., Schall, M. and Scheibel, A.B. 1993. A quantitative dendritic analysis of Wernicke's area. II. Gender, hemispheric, and environmental factors. *J. Comp Neurol* **237**, 97–111.

Kennard, M.A. 1940. Relation of age to motor impairment in man and in subhuman primates. *Arch Neurol Psychiatry* **44**, 377–97.

Kirschenbaum, B., Nedergaard, M., Preuss, A., Barami, K., Fraser, F.A.R. and Goldman, S.A. 1994. In vitro neuronal production and differentiation by precursor cells derived from the adult forebrain. *Cereb Cortex* **4**, 576–89.

Kolb, B. 1995. *Brain Plasticity and Behavior*. Mahwah, NJ: Erlbaum.

Kolb, B., Cote, S., Ribeiro-da-Silva, A. and Cuello, A.C. 1997a. NGF stimulates recovery of function and dendritic growth after unilateral motor cortex lesions in rats. *Neuroscience* **76**, 1139–51.

Kolb, B. and Elliott, W. 1987. Recovery from early cortical damage in rats. II. Effects of experience on anatomy and behavior following frontal lesions at 1 or 5 days of age. *Behav Brain Res* **26**, 47–56.

Kolb, B., Forgie, M., Gibb, R., Gorny, G. and Rowntree, S. 1998. Age, experience and the changing brain. *Neurosci Biobehav Rev*, **22**, 143–59.

Kolb, B. and Gibb, R. 1991. Environmental enrichment and cortical injury: behavioral and anatomical consequences of frontal cortex lesions in rats. *Cereb Cortex*, **1**, 189–98.

Kolb, B., Gibb, R., Gorny, G. and Whishaw, I.Q. 1997b. Possible regeneration of rat medial frontal cortex following neonatal frontal lesions. *Behav Brain Res* **91**, 127–41.

Kolb, B., Gibb, R. and van der Kooy, D. 1994. Neonatal frontal cortical lesions in rats alter cortical structure and connectivity. *Brain Res* **645**, 85–97.

Kolb, B., Stewart, J. and Sutherland, R.J. 1997c. Recovery of function is associated with increased spine density in cortical pyramidal cells after frontal lesions and or noradrenaline depletion in neonatal rats. *Behav Brain Res* **89**, 61–70.

Kolb, B. and Walkey, J. 1987. Behavioural and anatomical studies of the posterior parietal cortex in the rat. *Behav Brain Res*, **23**, 127–45.

Kolb, B. and Whishaw, I.Q. 1981. Neonatal frontal lesions in the rat: sparing of learned but not species-typical behavior in the presence of reduced brain weight and cortical thickness. *J Comp Physiol Psychol* **95**, 863–79.

Kolb, B. and Whishaw, I.Q. 1983. Dissociation of the contributions of the prefrontal, motor, and parietal cortex to the control of movement in the rat: an experimental review. *Can J Psychol* **37**, 211–32.

Kolb, B. and Whishaw, I.Q. 1996. *Fundamentals of Human Neuropsychology*, 4th edn. New York: W.H. Freeman & Co.

Leon, M. 1992. Neuroethology of olfactory preference development. *J Neurobiol* **23**, 1557–73.

Lois, C. and Alvarez-Buylla, A. 1994. Long-distance neuronal migration in the adult mammalian brain. *Science* **264**, 1145–8.

Rowntree, S. and Kolb, B. 1997. Blockade of basic fibroblast growth factor retards recovery from motor cortex injury in rats. *Eur J Neurosci* **9**, 2432–42.

Schanberg, S.M. and Field, T.M. 1987. Sensory deprivation stress and supplemental stimulation in the rat pup and preterm human neonate. *Child Dev* **58**, 1431–47.

Scheibel, A.B., Conrad, T., Perdue, S., Tomiyasu, U. and Wechsler, A. 1990. A quantitative study of dendrite complexity in selected areas of the human cerebral cortex. *Brain Cogn* **12**, 85–101.

Schulkin, J. (ed.) 1989. *Preoperative Events: their Effects on Behavior Following Brain Damage*. Hillsdale, NJ: Erlbaum.

Sirevaag, A.M. and Greenough, W.T. 1991. Plasticity of GFA-immunoreactive astrocyte size and number in visual cortex of rats reared in complex environments. *Brain Res* **540**, 273–8.

Solkoff, N. and Matuszak, D. 1975. Tactile stimulation and behavioral development among low-birthweight infants. *Child Psychiatry Hum Dev* **6**, 33–7.

Steward, O. 1991. Synapse replacement on cortical neurons following denervation. In *Cerebral Cortex*, Vol. 9, ed. A. Peters and E.G. Jones, pp. 81–131. New York: Plenum Press.

Weiss, S., Reynolds, B.A., Vescovi, A.L., Morshead, C., Craig, C.G. and van der Kooy, D. 1996. Is there a neural stem cell in the mammalian forebrain? *Trends Neurosci* **19**, 387–93.

Whishaw, I.Q., Pellis, S.M., Gorny, B.P. and Pellis, V.C. 1991. The impairments in reaching and the movements of compensation in rats with motor cortex lesions: an endpoint, videorecording, and movement notation analysis. *Behav Brain Res* **42**, 77–91.

Will, B. and Kelche, C. 1992. Environmental approaches to recovery of function from brain damage: a review of animal studies (1981 to 1991). In *Recovery from Brain Damage: Reflections and Directions*, ed. F.D. Rose and D.A. Johnson, pp. 79–104. New York: Plenum Press.